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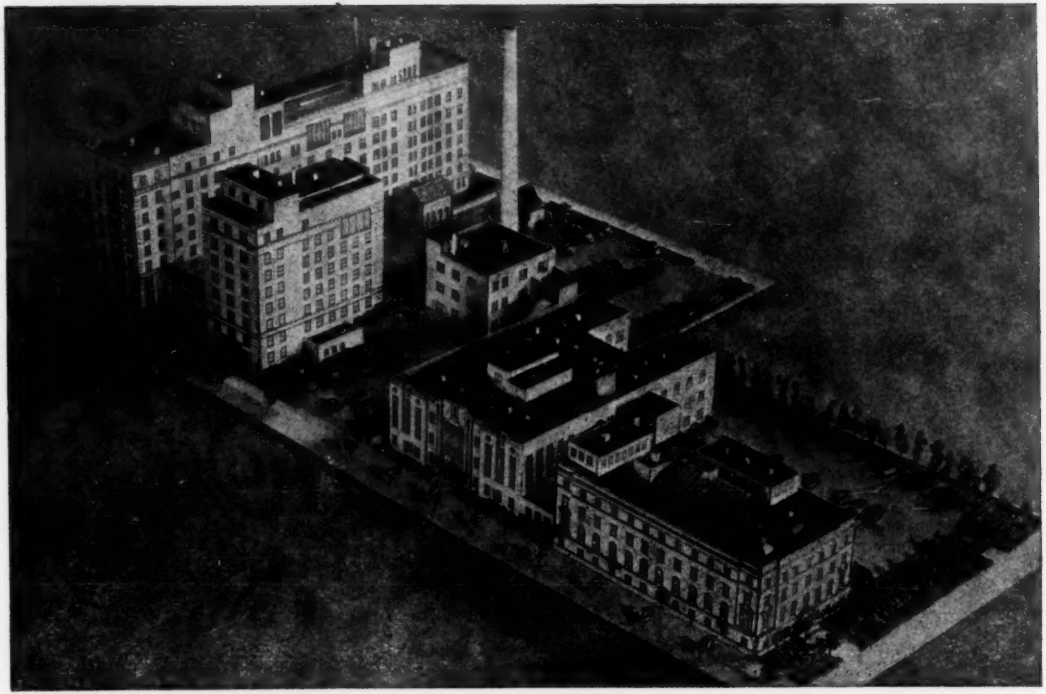

EXPERIENCES WITH THE SURGICAL TREATMENT OF HYPERTENSIVE CARDIOVASCULAR DISEASE IN MAN*

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Hypertensive disease, a frequent cause of premature disability and death, is an extremely complex problem and deserves the serious consideration of workers in all fields of medicine.

At the turn of the century, with the advent of a method for measuring blood pressure in human beings, hypertensive patients were divided into two main groups, those having some primary kidney disease and those having little or no evidence of kidney disease. The latter group is the larger, and to it the term essential hypertension is commonly applied. With this particular group we have been primarily concerned during the past twelve years.

The instability of the vascular bed in many hypertensive patients as observed by Hines and Brown[1] and others strongly suggested the participation of the autonomic nervous system in this disorder. Clinicians have long recognized that an outstanding characteristic of the blood pressure of many hypertensive patients is its unusual variability. As compared with the average normotensive person they are particularly sensitive to many stimuli, physical and mental. Accordingly, it is difficult to evaluate accurately the blood pressure of most of them. This variability suggested to Hines and Brown the need for a standard method of studying their blood pressure in order to detect these physiologic characteristics.

These workers described the hyperreactivity of the vascular bed to various stimuli, particularly to cold, and found that under resting basal conditions most hypertensive patients reacted to cold stimulus, such as immersion of one hand in ice water for one minute, by an excessive rise of both systolic and diastolic pressures (more than 20–15 mm. of mercury). They found that similar reactions occurred in about 15 per cent of normotensive persons, who because of unusual susceptibility to continued hypertension should be considered in the prehypertensive stage of the disorder. They collected evidence which suggested that this characteristic could be inherited and transmitted according to the mendelian

* Frank E. Bunts Institute Lecture.

law. They believed that in some instances hyperreactivity might be acquired in later life.

The surgical approach to hypertension in man is based on the role of the autonomic nervous system in cardiovascular disease, particularly in peripheral vascular disorders. Abolition of vasoconstrictor nerves to blood vessels of the extremities is followed by improvement in blood flow through the extremities and is of proved value in the clinical management of a variety of properly selected peripheral vascular disorders. Methods have been devised for selecting cases for surgery and for revealing the effect of surgical intervention upon the autonomic nervous system.

In approaching the problem of human hypertensive disease, it seemed advisable to obtain in a standard fashion data concerning blood pressure. This would be helpful in estimating the nature and severity of the hypertensive state of the particular individual, would reveal the underlying physiologic characteristics of the disorder, could be utilized in studying the effect of surgical procedures upon blood pressure, and might be helpful in selecting patients who would derive the greatest benefit from surgical treatment. Accordingly, a postural and cold test for blood pressure, a modification of the Hines-Brown cold test, was developed.

The data are obtained in a particular fashion. After two or three days of hospitalization, most of the time being spent in bed, the patient is taken to a quiet room and placed upon a comfortable bed. After a rest period of fifteen to twenty minutes, readings of pulse rate and blood pressure are taken at one minute intervals by a trained technician. Since the presence of a physician often acts as a pressor stimulus to hypertensive patients, and since, consequently, reflex responses may not be revealed, lower readings can be obtained by a technician, and abnormal reflex responses are more likely to be detected. Preliminary hospitalization and rest are also helpful in establishing the diagnosis of continued hypertension. Not infrequently a patient appears to have reached this stage of hypertension because ambulatory data indicate that the blood pressure is always elevated. It is surprising at times to find that, when studied in this fashion, the horizontal resting blood pressure may be normal, even in the presence of considerable cardiovascular disease as judged by the eyegrounds, the heart, or the kidneys.

The technic of testing is briefly as follows: Readings of pulse and blood pressure are taken every minute for five minutes, the patient first lying down, then sitting, then standing. During a rest period of five minutes in the horizontal position, readings are continued at one minute intervals. One hand is then immersed in ice water for one minute only,

and readings taken at the end of thirty seconds and one minute. After this readings are continued for five minutes. The patient then stands, and the cold test is exactly repeated (figs. 1, 2, 4, 5).

Blood pressure data are again obtained one year after operation and as often thereafter as possible. Postoperative data in the charts are cross-hatched. It was originally intended that the patients be hospitalized and studied exactly as before operation. Unfortunately, this has been impossible because of shortages of beds incident to the war. The data therefore are not strictly comparable. After operation the tests are made by appointment, with the patients ambulatory, and are carried out immediately after entrance to the hospital, with a preliminary rest period of fifteen to twenty minutes in the horizontal position.

Before discussing results, I shall comment briefly upon the extent of the operation we employ. Operative technics designed to denervate portions of the visceral vascular bed were devised by Adson, Craig, Peet, and Crile. Our first experience was with certain of these operations. We were impressed by anatomic variations in the autonomic nervous system, between patient and patient, as well as between two sides of the same individual. Consequently it occurred to us that, if one operation or another failed to modify hypertension, extension of the operation might convert failure into success. This was found to be true. Also, previous experiences with operation upon the autonomic nervous system, particularly for peripheral vascular disorders of the upper extremity, indicated that regeneration of interrupted vasoconstrictor pathways was possible and that hypertension might recur. This did happen in certain cases, and the recurrent hypertension was corrected by further surgery. Both considerations led to development of a more extensive operation, lumbodorsal splanchnicectomy.

The operation is performed in two stages eight to ten days apart. Its extent has been varied in order to determine the minimal effective procedure. It is not so extensive as the near-total sympathectomy of Grimson, the principal difference being that the heart is not denervated in the lumbodorsal procedure. The sympathetic trunks are removed at least from the tenth dorsal through the first lumbar inclusive, at most from the sixth dorsal through the third lumbar inclusive, and usually from the eighth dorsal through the first or second lumbar. In all cases the great splanchnic nerves are removed from the celiac ganglia to the midthoracic region. All divided rami are carefully clipped with silver dural clips to guard further against regeneration. As the operation became more extensive, there was physiologic evidence that the visceral vascular bed had been thoroughly denervated: Postural hypotension occurred in the acutely denervated state. This phenomenon is important,

principally because it indicates that important pathways have not been overlooked. Consequently, when the operation fails to modify the hypertensive state, one can be reasonably certain that inadequate surgery is not the explanation if postural hypotension was present immediately after operation. This makes it possible to evaluate other factors which might better explain the failure. Postural hypotension usually disappears in a few months, rarely being present at the end of a year. The magnitude and duration of the effect is related primarily to the extent of the operation into the lumbar region.

Results of operation are judged by the lowering of the diastolic blood pressure measured in the resting horizontal position one or more years after operation. Preoperative resting diastolic pressures ranged from 100 to 182 mm. mercury.

In a six year period over 600 unselected patients were operated upon, the great majority of operations being performed during the last three years. There were 36 deaths, a total mortality of 7.8 per cent. Operative mortality comprised 2.2 per cent; deaths within one year 2.0 per cent; and deaths one or more years after operation 3.6 per cent. These cases were reviewed to determine the circumstances under which poorer results could be expected. As a result, several rules were formulated to lower the mortality and to help in the selection of patients for operation.[1]

In one small group of men with resting diastolic levels of 140 mm. mercury or more the mortality was extremely high and accounted for nearly two-thirds of the total. Most of them had advanced eyeground changes and one or more of the following complications: cerebral accidents or encephalopathy, actual or impending congestive heart failure, or poor kidney function. Improvement was slight in three patients and pronounced in one. The remaining twenty odd patients in this group died. Operation seems inadvisable in such cases unless (1) there have been no cerebral accidents or attacks of encephalopathy, (2) the cardiac function is good, and (3) the renal function is normal or nearly normal. Under these circumstances one may hope to save an occasional patient without a prohibitive risk.

The majority of a series of 179 unselected patients observed for one to five years were improved. Favorable changes in eyegrounds, electrocardiograms, and cardiac and renal function, as well as improvement in the patient's general well being, were noted. In 42 per cent (group 1) the diastolic blood pressure was lowered 30 mm. mercury or more; in 18 per cent (group 2) 20 to 29 mm.; in 20 per cent (group 3) 10 to 19 mm.; and in 12 per cent (group 4) 0 to 9 mm. The blood pressure was higher in 8 per cent (group 5). In the first two groups (figs. 1, 2, 4, 5) the effect upon the blood pressure was obviously significant and was prob-

ably significant in the third. Certain patients in the fourth and fifth groups are clinically improved. In some, although there was no significant lowering of the diastolic level in the horizontal position, there were other changes such as lowering of peak levels after stimulation, generally associated with narrowing of pulse pressure and with a variable effect upon the magnitude of reflex responses. The latter may be absent, moderately reduced, or remain essentially unchanged.

The four characteristic effects of lumbodorsal splanchnicectomy are (1) lowering of diastolic levels, (2) narrowing of pulse pressure, (3) reduction in ceiling levels after stimulation, and (4) reduction in the magnitude of reflex responses. These changes in various combinations were noted in most cases after operation. The rules so far suggested have lowered the percentage of group 5 results but have made no significant difference in the others. These cases are being reviewed in order to determine the conditions under which one may be most certain that operation will be worth while. A larger series followed for a longer time will soon be available.

Certain general remarks may be made at this time regarding factors which appear to have a bearing upon the outcome. Results indicate that women are better subjects than men. From groupings made according to the width of the pulse pressure in the resting horizontal position, it is apparent that the wider the pulse pressure, the higher the percentage of poor results. Accordingly, we have divided the cases into three types. In type I (fig. 1) the pulse pressure is less than one-half the diastolic pressure. In type II (fig. 2) the pulse pressure is equal to, or up to 19 mm. mercury more than, one-half the diastolic pressure. In type III (figs. 4, 5) the pulse pressure is 20 mm. mercury or more greater than one-half the diastolic pressure. The highest percentage of better results is in type I women, in whom blood pressure was favorably modified to a significant degree in 81.8 per cent. The lowest percentage of better results was noted in the type III men, only 23 per cent of whom did well. The results in type II hypertension were between these extremes, again being better for women than for men.

In order to discuss the outlook for an individual patient with greater accuracy, other obvious factors must be considered. Thus patients must be further classified according to the preoperative resting diastolic level and also according to age. The age range so far is from 6 to 58, the average being a little under 40. It becomes apparent that the more variables that can be held constant, the more likely that one is dealing with similar forms and stages of human hypertensive disease. A large amount of data will be needed for such a detailed analysis. One certainly cannot group teen age hypertensive patients with those in the fifth decade, nor can

one group together cases of hypertensive disease of widely varying severity has judged by resting diastolic levels. There are many other factors to be considered: the state of the brain, eyegrounds, heart, and kidneys and the response to sedation. Likewise the duration of hypertension must be important, but the patient is rarely sure about this. We hope before long to consider some of these other factors, so that circumstances under which better results may be expected can be more accurately predicted.

An interesting aspect of this clinical investigation is the accumulation of data concerning the state of the renal arterioles in living hypertensive patients. The operative exposure permits gross inspection of the kidneys and the taking of biopsy material for microscopic study. Dr. Castleman described the changes and in patients with continued hypertension noted variation in arteriolar damage ranging from none to extremely severe. Biopsies are divided into five grades, 0 through 4. In grades 0, 1, and 2 changes are described as absent, minimal, and mild. Changes in biopsy grades 3 and 4 are regarded as moderate and severe respectively. Biopsy data also help to confirm the diagnosis of pyelonephritis in some patients and to establish it in others in whom it has not been suspected.

Renal blood flow data were obtained from small groups of cases representing the different biopsy grades. It was noted that, as the degree of arteriolar disease increased, renal blood flow decreased, ranging from normal in grade 0 biopsies to severe reduction in grade 4. Filtration fractions charted for the biopsy groups appear progressively to increase as the evidence of vascular disease increases. Filtration fractions were almost always normal in biopsy grades 0, 1, and 2 and elevated in most cases with biopsy grades 3 and 4. Biopsy grades of the two kidneys checked closely, as did split renal clearance determinations.

Approximately one half of the first 100 biopsies showed changes graded 0, 1, and 2. In the other half the changes were more severe, 3 and 4. We hoped that the result of operation might correspond to the degree of renal arteriolar damage as judged by biopsy material. However, the percentage of successes and failures in cases having biopsy grades 0, 1, and 2 was almost identical with that in those having biopsy grades 3 and 4. It is of interest to note that after operation, regardless of the effect upon the blood pressure, there is no significant change in either the quantity or nature of renal blood flow when measured in the resting horizontal position. It is also of interest that hypertension associated with known primary kidney disease, such as pyelonephritis, has been no less reversible than that without pyelonephritis.

The exposure in a lumbodorsal splanchnicectomy permits palpation and inspection of the adrenal glands. These appeared normal in the great majority of cases. In about 5 per cent tumors were found. These

were mostly cortical adenomas and varied in size from a few millimeters to several centimeters. Apparently the tumors and the hypertension are not closely related; for in most patients the response to excision of the tumor and unilateral splanchnicectomy was the same as in patients without tumors, that is, there was no effect upon the blood pressure.

Two patients with pheochromocytomas were exceptions to this statement. In each the hypertension responded so dramatically to removal of the tumor and unilateral splanchnicectomy that the tumor was undoubtedly the dominant factor. The physiologic characteristics of the hypertension in these two patients were identical. Both had severe continued nonparoxysmal hypertension of the narrow pulse pressure variety. Renal function was excellent, and biopsy material showed little or no evidence of renal arteriolar damage. Both had retinitis with severe retinal arterial changes. One had had a cerebral vascular accident and early congestive heart failure as well. The physiologic reactions of these patients during the preoperative postural and cold test were identical and very unusual when compared with those of most patients with so-called essential hypertension. Before operation both had postural hypotension associated with a definite increase in pulse rate. Both were hyporeactive to cold stimulation. There is little reason to doubt that in these patients the hypertension was mediated by a circulating humoral substance of an adrenalin-like nature. After operation the blood pressure returned to normal, and postural hypotension disappeared. Both continued to do well several years after operation.

SUMMARY

In summarizing these experiences with the surgical treatment of hypertensive cardiovascular disease in man, one is first of all favorably impressed by the objective improvement so far observed. It is evident that an adequate surgical procedure upon the autonomic nervous system is of real therapeutic value in the management of this disorder. From the viewpoint of the individual patient, it is important to determine the circumstances under which better results may be expected. Soon we hope to discuss this matter with particular reference to the accurate selection of cases.

It seems probable that this type of surgical intervention modifies hypertension specifically in a manner not similar, in our experience, to the effect of nonspecific operation. The explanation for the lowering of pressure has not been completely clarified and may be complex. In general, one suspects that smooth muscle tone is decreased, and that peripheral resistance to blood flow is thereby lessened. Whether this effect is solely the result of modifying neurogenic vasoconstriction or in

some way, as yet undetermined, the result of a modification of some humoral mechanism remains for the future to divulge.

The correct explanation for the success and failure of surgical treatment in human hypertensive disease may clarify causative mechanisms and may reveal in which respects human hypertensive disease resembles one form or another of experimental hypertension. Close cooperation between the clinician, the research worker, and the surgeon should hasten the solution of this problem.

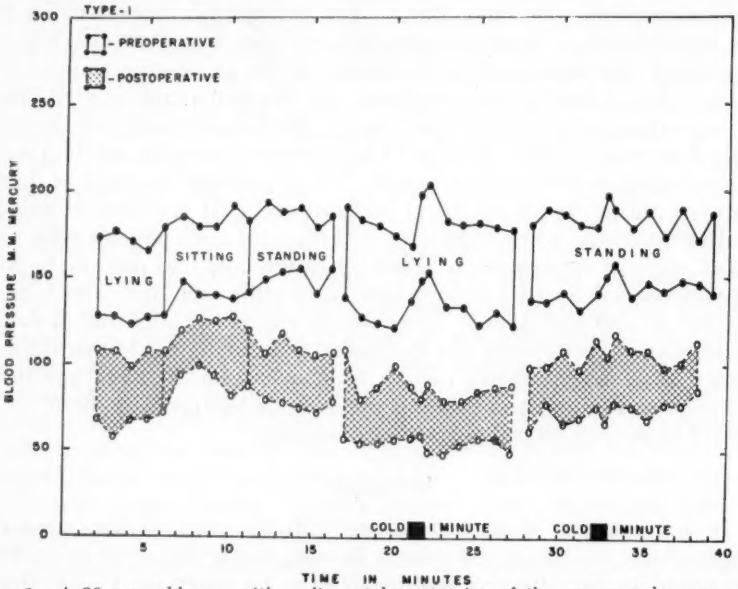

FIG. 1—A 36 year old man with malignant hypertension of the narrow pulse pressure variety (type 1) had grade 4 eyeground changes. Upon roentgen examination the heart was not enlarged or hypertrophied. The aorta was not tortuous. Electrocardiogram showed changes indicative of hypertensive and perhaps of coronary heart disease. Kidney function was normal by ordinary tests. Response to sedation was good, 130–90. Known duration of hypertension was two months.

Blood Pressure Data Before and Twenty-six Months After Operation

	Average		Ceiling Cold	
	Lying	Standing	Lying	Standing
Preoperative	175	189	204(36)	198(18)
(Resting)	128	152	154(18)	160(18)
Postoperative	106	109	90(2)	120(4)
(Ambulatory)	68	77	60(0)	80(2)

Twenty-six months after operation, patient was in excellent general condition and was symptomatically improved. Eyegrounds showed very pronounced improvement to normal, electrocardiogram showed definite improvement, and kidney function remained normal. Renal biopsies showed grade 4 arteriolar disease, changes comparable with those often seen in autopsy material. Physiologically, severe continued hypertension with hyperreactivity was significantly modified. He now may be classified as normotensive without hyperreactivity. All possible blood pressure changes after operation occurred in this case: (1) lowering of diastolic level, (2) narrowing of pulse pressure, (3) reduction in ceiling levels after stimulation by change of position and cold, (4) decrease in magnitude of reflex responses after stimulation. It is of interest that such definite improvement can take place in the most advanced renal arteriolar disease. (To help interpret this and subsequent charts, the average diastolic reflex response in our control series of normal individuals is plus 14 mm. mercury for changing from horizontal to upright position, plus 15 mm. mercury for cold stimulation in the horizontal position, and plus 12 mm. mercury for cold stimulation in the upright position.)

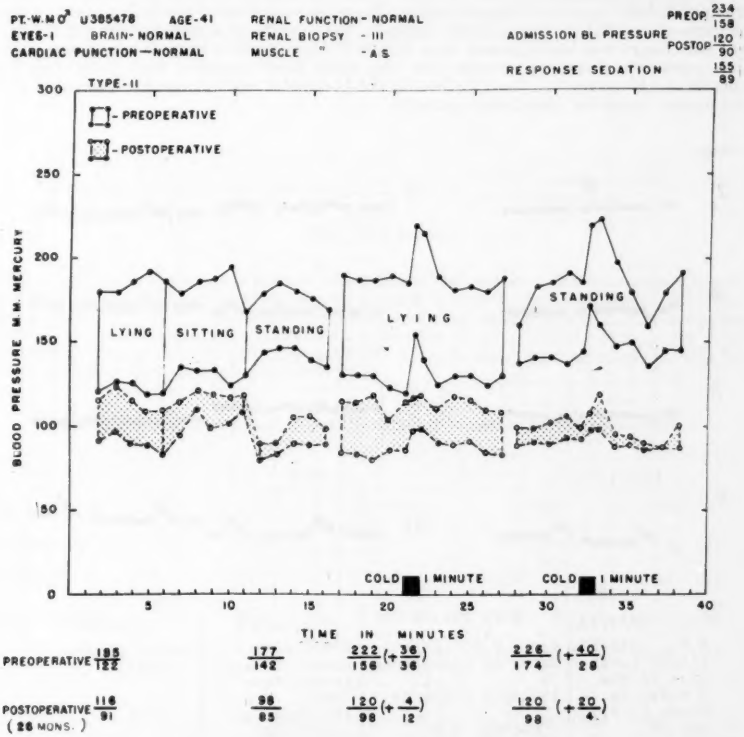

FIG. 2—A 41 year old man with severe essential hypertension of the intermediate pulse pressure variety (type II) had grade 2 eyeground changes, slight cardiac hypertrophy without enlargement. The aorta was not tortuous. Electrocardiogram showed changes illustrated in figure 3. Kidney function was normal by ordinary tests. Response to sedation was good, 155–89. Known duration of hypertension was nine years.

Blood Pressure Data Before and Twenty-six Months After Operation

	Average		Ceiling Cold	
	Lying	Standing	Lying	Standing
Preoperative.....	185	177	222(36)	226(40)
	—	—	— + —	— + —
(Resting).....	122	142	156(36)	174(28)
Postoperative.....	116	98	120(4)	120(20)
	—	—	— + —	— + —
(Ambulatory).....	91	85	98(12)	98(4)

Twenty-six months after operation the patient was greatly improved symptomatically. Eyegrounds were improved and normal. Electrocardiogram showed a completely normal tracing. Kidney function remained normal. Renal biopsies showed grade 3 arteriolar disease, changes of moderate severity. Physiologically, the hypertension was significantly modified, but the change was less dramatic than in case 1. Hypertension became less severe, and all four previously described changes that may occur after operation took place. (See footnote fig. 1.) However, the diastolic level in the horizontal position remained elevated above the normal range for ambulatory patients.

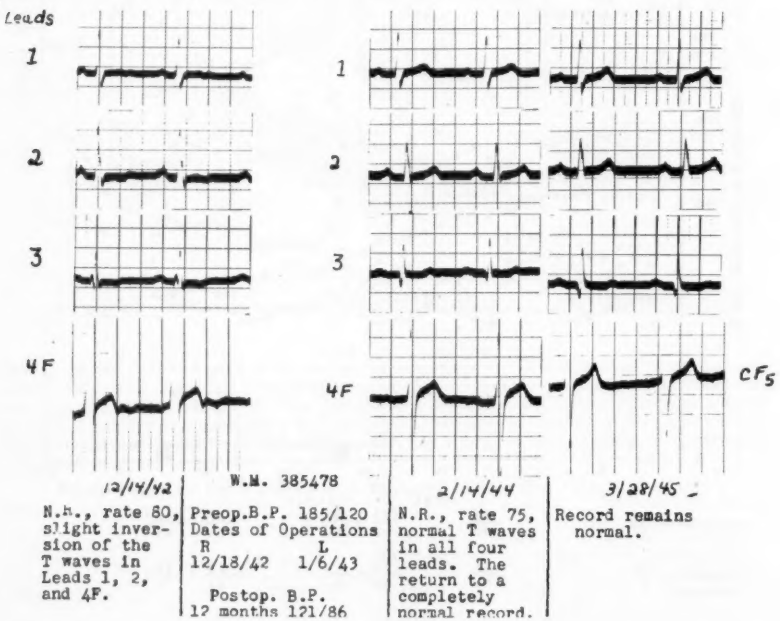

FIG. 3—(Same case illustrated in figure 2.) Prior to operation (December 14, 1942) the electrocardiogram showed normal rhythm, rate 80, slight inversion of T waves in leads 1, 2, and 4 F. One month after operation (February 14, 1944) the rhythm was normal, rate 75, and T waves were normal in all leads, a return to a completely normal record. Twenty-six months after operation (March 28, 1945) the record was normal.

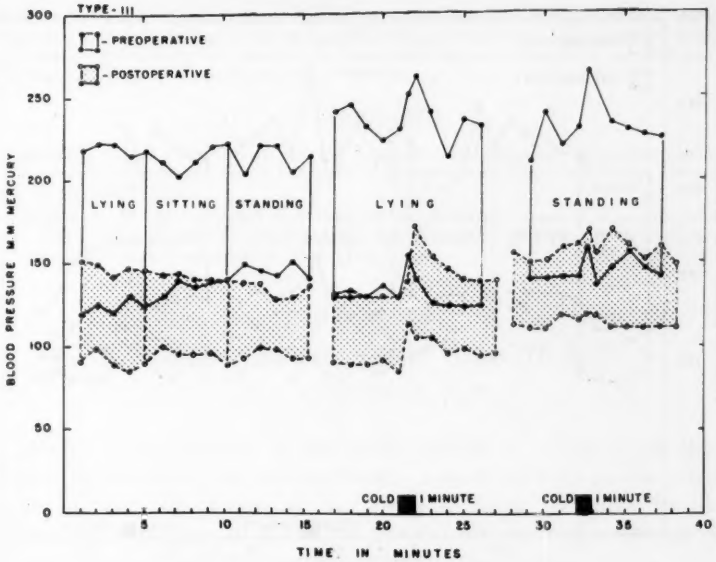

FIG. 4—A 48 year old woman with severe essential hypertension of the wide pulse pressure variety (type III) had grade 1 eyeground changes, a minor cerebral vascular accident, slight cardiac hypertrophy without enlargement, and good cardiac function. The aorta was tortuous. Electrocardiographic changes were indicative of hypertensive heart disease. Kidney function was normal by ordinary tests. Response to sedation was excellent, 120–70. Known duration of hypertension was two years.

Blood Pressure Data Before and Fourteen Months After Operation

	Average		Ceiling Cold	
	Lying	Standing	Lying	Standing
Preoperative	217	212	262(32)	264(34)
(Resting)	122	148	154(24)	158(18)
Postoperative	147	133	170(40)	168(6)
(Ambulatory)	90	95	114(30)	118(2)

Fourteen months after operation, patient felt much better. Eyegrounds showed no abnormality and were graded normal. Electrocardiogram was slightly improved. Kidney function remained normal. Renal biopsy material showed grade 3 arteriolar disease. There were no further cerebral accidents. Blood pressure was significantly modified; diastolic level was lower, and pulse pressure narrower; ceiling levels after stimulation were much lower. Reflex response to change of posture and to stimulation by cold when standing was reduced to within the normal range, but abnormal response to stimulation by cold in the horizontal position persisted. Diastolic level was not quite within the normal range for ambulatory patients.

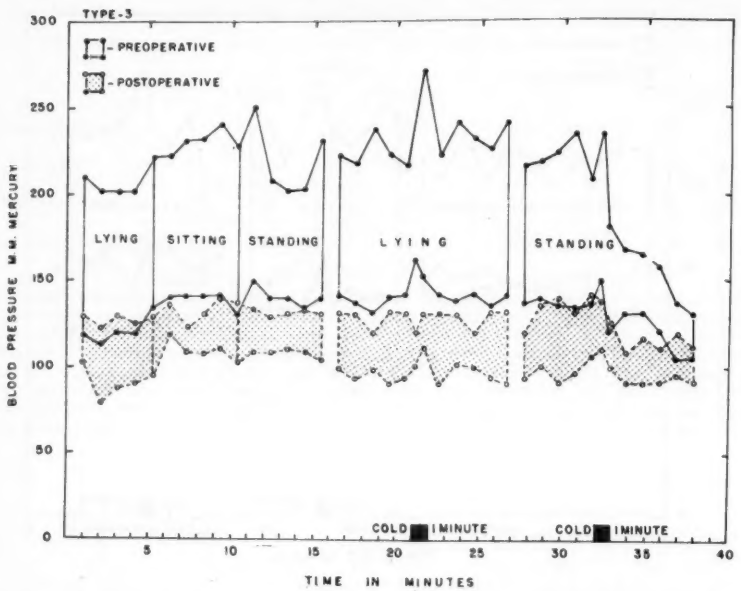

FIG. 5—A 27 year old woman had severe hypertension of the wide pulse pressure variety (type III) associated with bilateral chronic pyelonephritis. Kidneys were extensively scarred and contracted in an irregular fashion. Eyegrounds showed grade 2 changes. Upon roentgen examination the heart was not hypertrophied or enlarged, but the aorta was tortuous. Electrocardiogram showed changes indicative of hypertensive heart disease. Kidney function was normal by ordinary tests. Response to sedation was fair, 155–95. Known duration of hypertension was eleven months.

Blood Pressure Data Before and Thirteen Months After Operation

	Average		Ceiling Cold	
	Lying	Standing	Lying	Standing
Preoperative	204	215	270(56)	234(28)
(Resting)	120	139	160(30)	148(12)
Postoperative	127	131	130(0)	136(—16)
(Ambulatory)	92	107	110(16)	108(+2)

Thirteen months after operation the patient felt much better. Eyegrounds were improved but had not quite returned to normal, grade 1. Electrocardiogram had returned to normal. Kidney function remained normal. Renal biopsy material showed changes typical of pyelonephritis in scarred areas, chronic vascular nephritis grade 3 in nonscarred area of right kidney, and grade 4 in a similar area of the left kidney. Physiologic effect of operation was similar to that noted in the other cases. Hypertension was significantly improved but had

not reached normal. Known kidney disease, pyelonephritis, did not detract from the effect of operation. Results in our series of hypertensive patients with pyelonephritis, unilateral or bilateral, treated surgically have so far been the same as in those with so-called essential or malignant hypertension without pyelonephritis.

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EDEMA I

MECHANISMS OF EDEMA FORMATION

A. C. CORCORAN, M.D.

Edema is an excessive accumulation of fluid in extracellular spaces. It may be manifest, i.e., felt and seen; occult, located in the viscera; or latent, only demonstrable by chemical means. It may be local, as in inflammation or urticaria, or general and part of a systemic disturbance, as in congestive cardiac failure or nephritis.

Edema fluid may accumulate to the point where it interferes mechanically with tissue function or nutrition, so that what is at first an annoying sign of disease may later cause disability and death. Modes of relief of edema have therefore interested clinicians since the beginning of historic time. Since successful treatment depends primarily on identification and correction of the faulty mechanism, it is based largely on an understanding of physiology.

The purpose of the reports of which this is one is to review (I) mechanisms of edema formation, (II) clinical manifestations and consequences of edema, and (III) means of treatment.

BODY FLUIDS

The water of a unicellular organism lies within the cell; that of a multicellular organism is partitioned into intracellular and extracellular compartments. During life the membranous cell wall which separates intracellular and extracellular fluids is extraordinarily selective, so that these two fluids, although in constant shift and osmotic equilibrium, are chemically very different. Intracellular water is rich in salts of potassium; extracellular fluid has little potassium and much sodium, approximately 6 Gm. sodium chloride and 2 Gm. sodium bicarbonate per liter. The death of cells, as from burns, destroys membrane selectivity, so that sodium enters into cells and potassium leaves them.

Some 75 per cent of the body weight is water, intracellular fluid accounting for about 50 per cent of body weight and extracellular fluid for only 25 per cent. The mass of the intracellular compartment is greater. Cytophysiologically, it may be thought the more important, since its content must be rigidly maintained for cells to survive. From the aspect of the body as a whole, intracellular fluid is no more important than extracellular fluid from which it must ultimately be derived. As concerns the genesis, manifestations, and treatment of edema, extracellular fluid is the more important.

EXTRACELLULAR FLUID

In animals that possess a circulatory system, some of the sodium-rich extracellular fluid circulates rapidly as plasma, whereas about three quarters of it moves slowly as interstitial fluid and lymph. The capillary membranes which subdivide extracellular fluid into interstitial fluid plus lymph and plasma are freely permeable to water and salt, so that these occur in the two fluids in almost equal concentration. They are much less permeable to protein. Thus the protein content of interstitial fluid is small in comparison with that of plasma. The remaining solids occur in almost equal composition and concentration. Actually, the protein content of interstitial fluid varies with the organ in which it rests: That of subcutaneous tissues contains about 0.1 per cent protein; that of the kidneys 3 per cent; and that of the liver—where the vascular capillary endothelium is discontinuous—about 7 per cent, equalling that of plasma.[1]

These chemical characteristics as well as the anatomic position of extracellular fluid indicate its function and its phylogenetic history. It is the fluid medium in which the cell lives. Its content of sodium and other salts represents quite faithfully the sea water of Cambrian Age,[2] when supposedly the development of multicellular organisms began.

Extracellular fluid is formed from plasma by filtration under pressure in the arterial end of capillaries. As the hydrostatic pressure falls towards the venous end of the capillary, the osmotic pressure of the protein held within the capillary draws the fluid back into the venous end of the capillary.[3] There is thus a constant movement of interstitial fluid out of and back into the plasma under the opposing influences of hydrostatic (arteriocapillary) and osmotic (protein) pressure. The protein of interstitial fluid and that fraction of filtered water not reabsorbed into capillaries are removed in the lymphatics. The energy for this movement comes partly from the pumping action of muscle movement and partly from pulsation of arteries and arterioles.

Edema may arise whenever a failure in the *movement* of interstitial fluid causes more to be filtered into the tissues than is removed by capil-

laries and lymphatics. Edema may result from (1) wide arteriolar dilatation, which increases the filtration pressure in the capillaries—as when histamine is injected intradermally. (2) It appears when hypoproteinemia reduces the osmotic pressure of plasma proteins to such a degree that capillary reabsorption of interstitial fluid is inadequate. (3) An increase in venous pressure which greatly increases hydrostatic pressure at the venous end of the capillaries may cause edema by preventing reabsorption. Finally (4) edema may result from obstruction of lymphatic channels, and since in this instance the fluid which accumulates is rich in protein, its osmotic pressure soon balances that of the capillaries and creates a vicious cycle of increasing edema, e.g., elephantiasis.

Of the causes of edema which interfere with fluid movement, only two, hypoproteinemia and venous congestion, commonly cause generalized fluid accumulation.

Hypoproteinemia may result from severe protein deficiency. This may be dietary, as occurred in the prison camps of the Philippines, or alimentary, resulting from failure of intestinal function. Hypoproteinemia is a characteristic of chronic glomerulonephritis in the nephrotic stage and of nephrosis; to a lesser extent it is common in the eclamptogenic toxemias of pregnancy. In these diseases it is usually associated with severe albuminuria. If albuminuria is very profuse and the protein in the diet too rigidly restricted, part of a seemingly "nephrotic" hypoproteinemia may be nutritional and may be relieved by correcting the dietary deficiency. More commonly hypoproteinemia which accompanies renal disease cannot be relieved by adequate administration of protein in the diet or by transfusion. It is seemingly due to a change in the "set" of the control which regulates plasma protein content. Although evidence at hand suggests that hypoproteinemia in renal disease may be a homeostatic protective device, which acts to maintain urine formation by lowering the colloid osmotic pressure of the blood, the mechanism of this alteration is not clear.[4] Such hypoproteinemia varies with the course of the renal lesion and cannot be altered by changing the diet.

In congestive cardiac failure venous congestion is believed to participate in the edema. It is not the whole explanation, since in congestive cardiac failure the rise of venous pressure more often follows than precedes the onset of edema.[5] Also many patients with cardiac disease suffer from some degree of nutritional hypoproteinemia.

Thus, apart from hypoproteinemia, mechanical failure of interstitial fluid movement is only rarely and then terminally a cause of generalized edema. Rather the origin of edema in early congestive cardiac failure must be sought in the operation of controls of extracellular

fluid volume and content. The basic fact that determines shifts in body fluid is that changes in the osmotic concentration of ions in extracellular fluid may seriously interfere with cellular function by demanding a corresponding adjustment in the intracellular fluid.[6] Therefore attempts at changes in osmotic concentration of extracellular fluid are vigorously resisted by the controls, principally renal, which regulate the volume and content of extracellular fluid. In a tendency toward a change in electrolyte content of extracellular fluid, these controls act by altering the volume of this fluid to preserve its concentration. Thus, in sodium retention the body retains water and increases the extracellular fluid volume, even to the point of edema, to maintain its normal concentration. Such edema has no functional significance apart from the mechanical stresses it may impose, whereas were sodium retention not followed by edema, hypernatremia might result in death. To the extent that retention of water can balance retention of sodium and so preserve the electrolyte concentration of extracellular fluid, formation of edema is protective.

That the body responds more actively to changes in concentration than to changes in volume of extracellular fluid is easily shown. Ingestion of a fluid corresponding osmotically to interstitial fluid, such as 0.9 per cent sodium chloride, does not cause diuresis, for the fluid is retained. On the other hand, ingestion of water is countered promptly by diuresis, and excessive intake of salt is met at first by water retention. Conversely, salt deprivation results in water loss and shrinkage of interstitial fluid volume, and a water deficit is followed by salt loss and a corresponding diminution of interstitial fluid volume. In either of the latter instances the subcutaneous tissues lose their turgor, and the appearance is that of dryness and dehydration. Actually, what is lacking is not water, as the bastard word *dehydra*tion implies (L. *de* away Gr. *hydor* water), but rather extracellular fluid, which is a dilute alkaline brine. Such fluid loss is treated by administering physiologic saline and trusting to renal activity to excrete the excess chlorine and retain the needed sodium, or by giving a balanced mixture of sodium chloride and sodium lactate or bicarbonate.[7] Such a change is the exact opposite of edema in which salt in water, not water, is retained in excess.

SODIUM RETENTION

Thus the problem of generalized nonhypoproteinemic edema resolves itself into one of simultaneous retention of water and sodium ions. If water is retained, salt must be; if salt is, water must be In either case edema, at first latent and hypostatic and later manifest and generalized, develops. Of the two components of edema fluid, water is the more

readily disposable and less easily retained, since it has three pathways of excretion—respiratory, cutaneous, and renal. Salt, however, is largely excreted through the kidneys. A priori, sodium retention is of more significance than water retention in the genesis of edema.

Since sodium is not rapidly excreted, sodium retention and edema may result from an excessive and rapid intake of salt. When the intake of sodium is not excessive and the movements of interstitial fluid are normal, then sodium retention and edema can only result from failure of sodium excretion.

Such a failure of sodium excretion may be due either to functional or structural changes in the principal excretory apparatus, the kidney. Normally, plasma water contains about 580 mg. sodium chloride per 100 ml., and about 125 ml. of this fluid (720 mg. sodium chloride) is filtered per minute through the glomerular capillaries into the renal tubules. Thus about 1100 Gm. of salt a day is filtered off from the blood; of this only 5 or 10 Gm. appears in the urine. The 99 per cent difference between filtration and excretion of salt represents the activity of the renal tubules in reabsorbing salt from tubular fluid into the blood. Normally, an increased bodily need for salt is met by increasing — although to a very slight degree, for the control is already fixed near its maximum—salt reabsorption until all but the obligatory minimum (about 0.1 per cent) of salt remains. A hypothetical total tubular defect of reabsorption with loss of a kilogram of salt daily would require the excretion of about 80 liters of water, since the ceiling concentration of salt in the renal tubules is about 1.5 per cent.

Salt reabsorption is partly controlled by the secretion of the adrenal cortex; deficiency of its salt-retaining elements, as in Addison's disease, results in sodium loss and shrinkage of extracellular fluid. In this situation the control is lost while the mechanism remains intact. When the kidney is structurally diseased, the situation is reversed. If the damage is chiefly glomerular, and the tubules are well preserved, filtration rate is reduced, say to 50 ml. carrying 290 mg. of salt a minute; the tubule cells, seemingly unaware that half the salt which should have been filtered is being retained in the body, take back a normal absolute amount of salt from the small volume of tubular fluid presented to them. Salt retention results. Such deficient filtration with active reabsorption seems to account for much of the edema of acute glomerulonephritis and of eclampsia and pre-eclampsia. More commonly both tubule and glomerulus are diseased, and the presence or absence of edema will then be determined by the preponderance of lesions, the dietary stresses, and levels of plasma protein. Seriously damaged tubule cells are incapable of reabsorbing salt or of responding normally to bodily demands; through injured

glomeruli at least some filtration of salt and water continues. The result may be salt loss, shrinkage of extracellular fluid, and ultimately hyponatremia and dehydration with consequent disturbances of renal and cellular function. Thus, uncontrolled renal disease may result in salt loss with shrinkage of extracellular fluid or salt retention with edema. Because the renal control is defective, the margin between these extremes, which in health is wide, may in disease be very narrow.

However, the commonest cause of clinical edema is not renal disease, with salt retention or with hypoproteinemia or with both, but congestive heart failure. The mechanism of edema in congestive heart failure is not clear. It was once supposed, largely from the analogy between congestive failure in man and heart failure in the isolated heart-lung preparation, that edema results from a combination of increased venous pressure, which would tend to decrease reabsorption of interstitial fluid, and an anoxic increase in capillary permeability, which would increase its formation. Cardiac edema would thus be due to deficient *movement* of extracellular fluid. Actually, congestive failure may be well advanced before either venous pressure rises significantly or arterial oxygen content is notably reduced.[5] However, in many patients with heart failure there is a great reduction of renal blood flow, which disappears as heart failure is relieved.[8] This decrease of renal blood flow is vasoconstrictive and is associated with a decrease in glomerular filtration rate. Therefore it is suggested that the edema of congestive heart failure, as does that of acute glomerulonephritis, arises in renal failure of salt excretion due to functional rather than to structural change.

From the aspect of treatment, which will be discussed later in detail, the fact that edema fluid, however formed, must contain sodium has the corollary that sodium deprivation must prevent its formation and cause its reabsorption.

SUMMARY

Edema is an excessive accumulation of interstitial fluid. Its cause lies either in failure of the normal mechanisms of movement of this fluid (mechanical, vascular, lymphatic, and hypoproteinemic edema) or in the operation of controls which protect the body from changes in concentration of electrolytes, principally sodium, in interstitial fluid by permitting changes in volume. The specific stimulus which commonly provokes fluid controls to permit edema formation is sodium retention. Sodium retention is therefore often the key to the origin of generalized edema. Since the principal site of sodium excretion is the kidney, sodium retention is therefore associated with functional or structural disturbances of renal function. In either case, restriction of dietary sodium below the minimal level of sodium excretion must ultimately result in loss of water and salt and therefore in correction of edema.

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CARCINOMA COMPLICATING ULCERATIVE COLITIS

Report of Two Cases

R. J. F. RENSHAW, M.D., AND T. S. BROWNELL, M.D.

Because the complication seemed to be uncommon, we have reviewed our experience with carcinoma complicating ulcerative colitis. Between 1934 and 1943 one of us saw 2 cases of carcinoma in 336 cases of ulcerative colitis. This was an incidence of 0.59 per cent. During the same period 1608 cases of carcinoma of the colon were seen at the Cleveland Clinic.

Because both patients herein reported were under 30 years of age, our attention was directed to this age group. One per cent (17 cases) of all cases of carcinoma of the colon and 38 per cent (128 cases) of all cases of ulcerative colitis occurred in persons under 30. In this same age group the incidence of carcinoma of the colon with chronic ulcerative colitis (1.5 per cent) was slightly higher than the incidence without ulcerative colitis (1 per cent).

Ewing[1] considered it significant that carcinoma rarely occurred in ulcerative colitis. Matzner and Schaefer[2] reported 1 case of carcinoma complicating ulcerative colitis. The patient was a 29 year old man. Yeomans[3] reported 7 cases of malignant neoplasm developing in rectal adenoma, 1 of which occurred with ulcerative colitis. This patient was a 33 year old woman. Hurst[4] stated that an adenomatous polyp might become malignant and that carcinoma might complicate ulcerative colitis, but that most malignant adenomas were not secondary to or associated with colitis. Swinton and Warren[5] stated that they had not observed progression of polypoid changes in ulcerative colitis to malignant disease. On the other hand, Ganshorn[6] demonstrated a greater frequency of carcinoma in the presence of adenomatous hyperplasia of the

mucous membrane. In 217 patients of all ages with ulcerative colitis Streicher[7] found an incidence of carcinoma of 1.2 per cent. Bockus[8] observed 3 cases in approximately 200, an incidence of 1.5 per cent.

A higher incidence of carcinoma has been found by Bargen and his colleagues, who have had extensive experience. Since the beginning of the study Bargen has seen 54 cases of carcinoma complicating ulcerative colitis.[9, 10, 11, 12] He also advised one of us that since his last report[9] he has seen six additional cases. He further believes that carcinoma complicating ulcerative colitis is occurring with increasing frequency.[13] In 1929 he reported an incidence of 2.5 per cent in 693 cases of ulcerative colitis,[10] and in 1938 a 3.2 per cent incidence in 817 cases.[11]

Jackman, Bargen, and Helmholtz[14] in a study of 95 children with ulcerative colitis reported the highest incidence of carcinoma, 6.3 per cent. The reason for this unusually high figure is not clear to us. According to Bockus[8] these statistics might indicate that ulcerative colitis predisposed to the development of carcinoma and that conceivably adenomatosis was the initial lesion in some of the children. Bargen[12] ventured the opinion that the severely destructive process of colitis might exhaust the tissues' reparative ability and precipitate a wild growth of cells. This theory applied to children in an active growth phase might explain the higher incidence of carcinoma complicating ulcerative colitis.

Polyposis is generally conceded to be the most common complication of ulcerative colitis (10 per cent). It is a pseudopolyposis consisting of mucous membrane tags after healing has taken place or of islets of mucous membrane between areas of ulceration. As shown by Coffey and Bargen[15] one must clearly differentiate between polyposis and adenomatosis. They found a 62.5 per cent incidence of carcinoma in adenomatosis, whereas in multiple polyposis complicating ulcerative colitis the incidence was only 25 per cent, which is higher than most workers report. It is generally believed that the polyposis of ulcerative colitis is not related to adenomatosis and shows no greater tendency to undergo malignant change than normal mucosa.

CASE REPORTS

Case 1—A white man, aged 22, was seen in the clinic in November 1935. The previous April he had an appendectomy for an attack of lower right quadrant pain. Shortly thereafter he had diarrhea of eight to ten stools a day and an afternoon fever of 102 to 103 F.

Examination of the rectal mucosa revealed changes typical of chronic ulcerative colitis. Occult blood and pus but no parasites were found in a stool examination. Stool cultures showed nonhemolytic streptococci, Staphlococcus albus, and gram-negative bacilli. Roentgenologic examination revealed that ulcerative colitis involved the entire colon. The erythrocyte count was 4,730,000, leukocyte count 11,000, and hemoglobin 12.0 Gm. per 100 ml. blood.

The patient, who was seen in the clinic only a few times in the succeeding nine year period, received various types of treatment elsewhere. In October 1944 he returned complaining of sharp, stabbing pains across the upper abdomen and for the preceding five weeks of an increase in the number of stools daily.

In the right upper abdominal quadrant was a palpable, poorly defined, firm, smooth mass, which did not move with respiration. By proctoscopic examination the rectal mucosa was found to be granular. It bled only slightly when swabbed. At the level of the prostate gland was a localized area of pseudopolyposis. Roentgenologic examination showed that ulcerative colitis involved the entire colon. A large irregular filling defect involved the hepatic flexure and proximal colon (fig. 1).

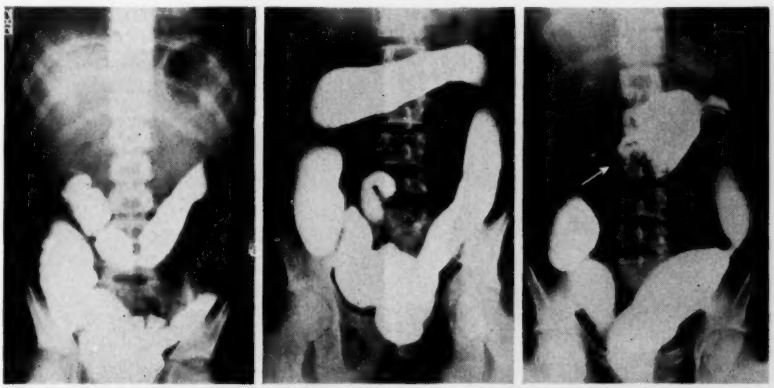

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FIG. 1 (Case 1)—(a) Appearance of colon in 1935 when the patient was first seen in Clinic. (b) Appearance of colon in 1940. (c) Appearance of colon in 1944. Filling defect and obstruction at site of arrow.

A right colectomy was done. Pathologic examination disclosed an ulcerated, polypoid, mucinous adenocarcinoma of the hepatic flexure and ascending colon. There was invasion of the colon wall with direct extension into paracolic areolar tissue, involvement of lymphatics and venules, and metastasis to regional lymph nodes. There was also focal, acute, ulcerative, widespread, chronic inflammation of the ileum, cecum, and ascending and transverse colon, with atypical polypoid hyperplasia and multiple polyps.

The patient died at home a few months later. No autopsy was performed, and the immediate cause of death could not be ascertained.

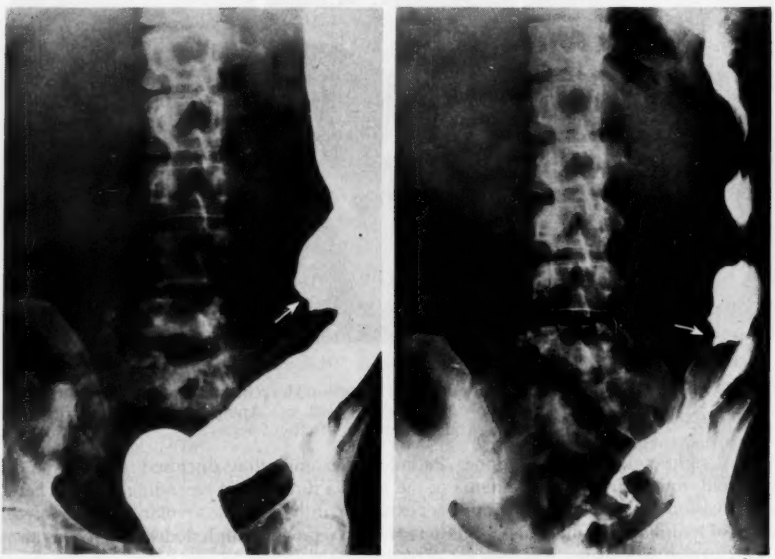
Case 2—A white housewife, aged 27, was seen in the clinic in February 1941. During the preceding nine years she had three to four loose bloody stools daily, and a diagnosis of chronic ulcerative colitis was made in a university hospital. Two or three weeks before admission to the clinic she had cramping pains, soreness of the abdomen, borborygmi, bloating, and fever.

The patient was poorly nourished and toxic. The temperature was 100 F. The abdomen was distended, and the superficial veins were dilated. A visible and palpable mass filling the epigastrium and right upper quadrant and extending to the iliac crest on the right was thought to be a nodular, enlarged liver. A fibrous stricture of the rectum was found about three inches from the anus, beyond which the proctoscope could not be inserted. The mucous membrane between the anus and the fibrous band was edema-

tous and had the typical appearance of severe advanced ulcerative colitis. There were multiple ulcers and a profuse mucopurulent discharge. The mucosa was friable and granular and bled easily.

Laboratory examination revealed 2 plus amounts of albumin in the urine, 5,800,000 erythrocytes, 14.9 Gm. hemoglobin per 100 ml. blood, and 17,500 leukocytes with 70 per cent polymorphonuclear neutrophils and 30 per cent lymphocytes. The icterus index was 13. Wassermann and Kahn reactions of the blood were negative. No parasites were found in the stools.

Roentgenologic examination of the colon showed pronounced narrowing of the rectum just proximal to the anus in the region of the inflammatory stricture seen through the proctoscope. In the midtransverse colon an obstructing lesion was demonstrated (fig. 2).



a *b*

Fig. 2 (Case 2)—(a) Obstructing lesion in transverse colon beyond which barium enema could not be forced. (b) Postevacuation film. Large liver extends almost to iliac crest.

On the basis of these findings a diagnosis was made of ulcerative colitis and carcinoma of the transverse colon with metastasis to the liver. Confirmation of this diagnosis was not possible by microscopic section, but clinically there was no doubt as to the presence of a malignant neoplasm.

The patient refused peritoneoscopy and exploratory laparotomy and was discharged on medical management. She died at home three weeks later.

SUMMARY

Carcinoma of the colon complicating chronic ulcerative colitis as observed in the Cleveland Clinic is uncommon in adults. Only 2 cases

were encountered in a nine year period, which was an incidence of 0.59 per cent of all cases of chronic ulcerative colitis and of 1.5 per cent of cases occurring in patients under 30 years of age.

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MODIFICATIONS IN THE ROURKE-ERNSTENE SEDIMENTATION RATE METHOD

L. W. DIGGS, M.D.

The Rourke-Ernstene method[1] for determination of sedimentation rate measures the sinking velocity of erythrocytes during the period of most rapid fall. This method is considered to be more accurate than those that utilize a single one hour reading,[2] such as the Wintrobe, Cutler, and Westergren methods. Other advantages of the method are the following: A small volume of blood (1.5 ml.) is required, the volume of packed red blood cells can be determined, and correction for anemia

based upon the hematocrit reading can be calculated. The Rourke-Ernstene tube is preferred to the Wintrobe tube because it is longer and has a wider lumen. The greater length delays the "packing phase," and the increased width makes the tube easier to clean and to fill.

In the original Rourke-Ernstene method heparin was used as an anticoagulant. For this the dry potassium and ammonium oxalate mixture of Heller and Paul[3] has been substituted in the Cleveland Clinic, because the oxalated mixture is more economical, more dependable, and simpler to prepare. Various workers have shown that the results are comparable with those obtained with heparin.[2,4]

Rourke and Ernstene recommended recording the time-distance readings, constructing a curve from these readings, and calculating the fall of erythrocytes in millimeters per minute from the slope of the straight-line portion of the graph. Estimation of the sedimentation rate from graphs proved to be too time-consuming for clinical use. The modifications first made and for years used by our laboratory were (1) the determination of the time required for the top of the red cell column to reach successive 2 mm. marks on the tube and for the rate to become constant and (2) the computation of the sedimentation rate directly from these figures.

Ham and Curtis[2] estimated that there was an error of approximately 2 per cent in the sedimentation rate as determined by the Rourke-Ernstene method on duplicate specimens when only a few specimens were examined. In order to determine the accuracy of the procedure under clinical conditions when multiple tubes were simultaneously observed, venous bloods from 41 unselected clinic patients were placed in duplicate vials and sent to different laboratories for sedimentation rate estimation. Six or more tubes comprised each group. In 65 per cent of the tests the difference in final reading corrected for anemia was 0.2 mm. a minute or less, in 17 per cent the discrepancy in results was between 0.21 and 0.4 mm. a minute, and in 17 per cent 0.4 mm. a minute or more (table). Differences of this magnitude are not clinically significant when the sedimentation rate is very rapid, but in borderline cases such discrepancies lead to errors in interpretation.

The lack of correlation in readings made at 2 mm. intervals is in part due to the physical impossibility of focusing the eye on multiple points at the same time and of recording the exact moment when numerous falling columns, all proceeding at different rates, arrive at given lines. Other errors are due to failure to take fractions of a minute into consideration, to lack of sharp demarcation between plasma and top of erythrocyte column, to the thickness of the lines, and to reading the column a little above or below the line.

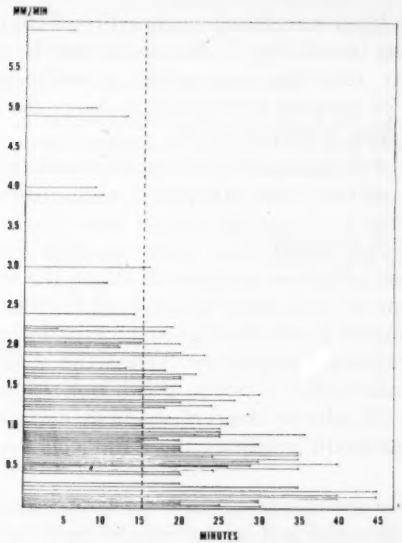

FIG. 1—Duration of "intermediate phase" of sedimentation rates in 70 specimens arranged according to uncorrected sedimentation rate.

Another disadvantage in making time-distance readings at 2 mm. intervals is that the technician has to watch the blood continuously from the time the tubes are filled until all tests are completed. During a given "run" she cannot perform other laboratory tasks.This leads to inefficient use of the technician's time. Because the test once started demands the technician's undivided attention, a group of tests cannot be started until multiple specimens have accumulated. This delay leads to error; for the sedimentation is retarded when blood is allowed to stand for several hours.

In order to maintain the advantages of the Rourke-Ernstene procedure and to make the testing more accurate and practical under conditions in which multiple tests have to be done, the results obtained from readings made at longer intervals were studied.

The duration of the period of most rapid fall was analyzed using graphs of sedimentation rates of 70 patients, each graph being plotted from frequent time-distance readings.* This was done by noting the time between the end of the "aggregation phase," characterized by a sharp dip in the slope of fall, and the beginning of the "packing phase," characterized by flattening out of the curve. The duration of the "inter-

* Electrophoresis Laboratory, Dr. Lena Lewis.

mediate phase" is longest in slowly sedimenting bloods and shortest in rapidly sedimenting bloods (fig. 1). Readings must be made at 5 minute intervals or less to cover the entire range of sedimentation rates, but intervals of 15 to 20 minutes were found to cover the majority of cases with a rate of 1.5 mm. a minute or less.

The maximal sedimentation rate as determined by the standard Rourke-Ernstene method was compared with maximal rates determined from readings at 15 and 20 minute intervals. Graphs were analyzed of 115 unselected bloods from clinic patients. Scatter diagrams of the results obtained are given in figure 2. When the sedimentation rate is 1 mm. a minute or less, these show good correlation between the maximal rate obtained from readings at 15 minute intervals and from readings by the standard procedure. When the sedimentation rate is more rapid, the correlation is not so good, but this is of little clinical significance. The 20 minute interval readings correlated less satisfactorily with the standard readings than did the 15 minute interval readings (fig. 2).

The accuracy of sedimentation rate determinations using 15 minute interval readings was checked by having different technicians examine duplicate specimens. Six or more bloods were examined simultaneously. In 54 observations checks within 0.2 mm. a minute were obtained in

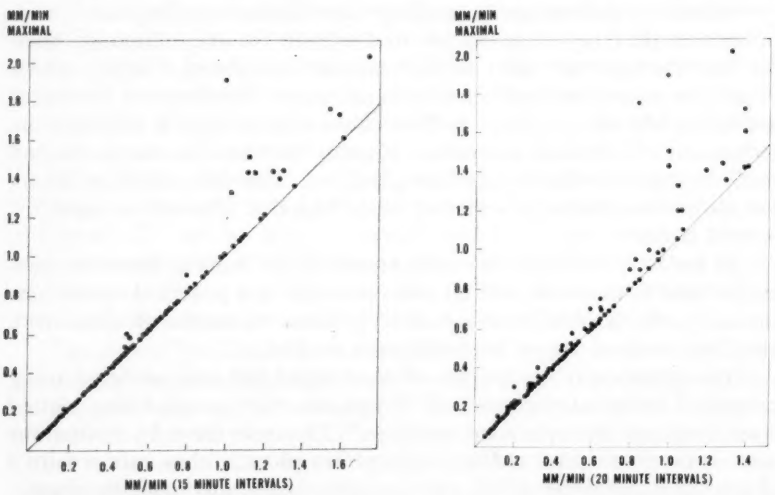

FIG. 2—Scatter diagram showing correlation between maximal sedimentation rate and rate calculated from maximal fall during 15 minute and 20 minute intervals.

80 per cent of the cases. In no case was the difference greater than 0.4 mm. a minute. These results were much better than those obtained from readings made at 2 mm. intervals (table).

TABLE—Variation in sedimentation rate corrected for anemia as determined by different technicians on duplicate specimens of oxalated blood. Rourke-Ernstene tubes used. Six or more bloods examined simultaneously.

Number of examinations	Method	Difference in sedimentation rate (% of total number)		
		0.0-0.2 mm./min.	0.21-0.4 mm./min.	0.4+ mm./min.
41	2 mm.-time readings until fall constant	65	17+	17+
54	Maximal fall/15 min. intervals	80	20	0

On the basis of these studies it seemed justifiable to modify the Rourke-Ernstene method for clinical use by making the readings at 15 minute intervals. Technicians who have had long experience with the standard method and who also have used the 15 minute interval method find the latter procedure much less exacting. They also have sufficient time between readings to clean pipets, to make centrifuge readings, to get out reports, and to perform other essential tasks.

METHOD

The method now used at the clinic for determining the sedimentation rate may be summarized as follows:

Equipment and Supplies

1. Rourke-Ernstene tubes, length 12 cm., internal diameter 4 mm., calibrated at 2 mm. (Macalaster and Bicknell, Cambridge).
2. Straight shell vials, 35 by 12 mm., with cork stoppers, calibrated by scratching side of tube at 1.5 mm. mark.
3. Capillary pipets with rubber bulbs for filling and cleaning tubes.
4. Anticoagulant mixture containing 2 Gm. potassium oxalate and 3 Gm. ammonium oxalate in 100 ml. distilled water; 0.06 ml. is placed in each vial and evaporated to dryness in the incubator.

In the vial is placed 1.5 ml. venous blood, which is thoroughly mixed with the dried oxalate. The specimen is sent to the laboratory with an identifying slip. The specimen is vigorously agitated for at least one

minute. The blood is then taken up by means of the capillary tube, and the Rourke-Ernstene tube is filled to the 0.0 mark. Care is taken to avoid air bubbles. Laboratory request slip is numbered to correspond to number on tube.

The tubes are hung in a special rack made of a sheet of stainless steel with a series of ¼ inch holes suspended over a viewing box. This has an opaque glass window and indirect lighting supplied by a linear fluorescent light (fig. 3).

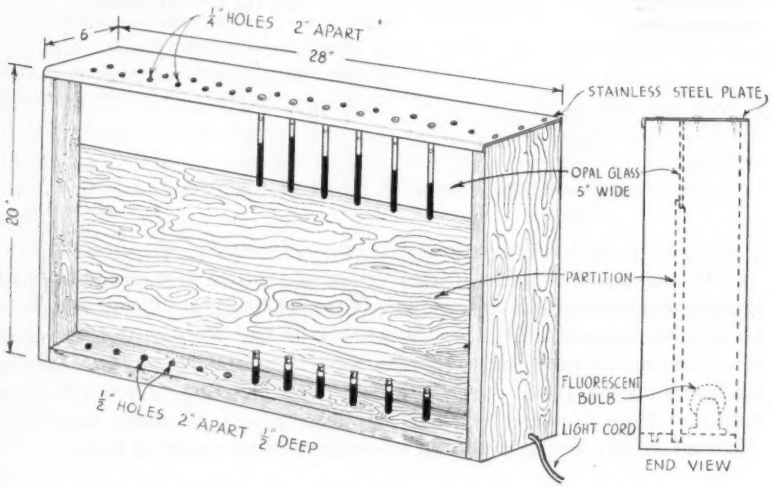

Fig. 3—Illuminated suspension rack for Rourke-Ernstene tubes.

Readings are made every 15 minutes, four readings being made on each tube. The most rapid fall during any 15 minute interval is considered representative of that sample. The millimeter fall during this most rapid quarter hour interval divided by 15 gives the rate in millimeters per minute. Since the sedimentation rate is usually most rapid in the third and the fourth and seldom in the first interval, and since the point of beginning the observation in relation to the filling of the tube is arbitrary, no attempt is made to note the time of filling each tube. The tubes are filled as soon as possible after the blood arrives at the laboratory, but readings are made every 15 minutes, preferably on the hour and 15, 30, and 45 minutes after the hour.

After the sedimentation rate has been noted, the tubes are placed in a centrifuge and spun to a constant pack. The volume of packed cells is read, and the sedimentation rate corrected for anemia according to

the Rourke-Ernstene chart.[1] The final report includes the uncorrected and the corrected sedimentation rate in millimeters per minute and the hematocrit reading.

SUMMARY

1. The Rourke-Ernstene sedimentation rate method is made more practical and, under conditions where multiple tests have to be performed simultaneously, more accurate by the following modifications now used at the Cleveland Clinic:

a. Substitution for heparin of the dry potassium and ammonium oxalate mixture of Heller and Paul.

b. Estimation of the sedimentation rate from readings at 15 minute intervals rather than from graphs of time-distance readings or from direct calculations made from 2 mm.-time readings.

c. Use of an illuminated rack for suspending Rourke-Ernstene tubes.

2. When 54 duplicate specimens of blood from unselected clinic patients were examined, the sedimentation rate calculated from readings at 15 minute intervals and corrected for anemia checked within 0.4 mm. a minute.

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PRIAPISM IN LEUKEMIA

Report of Two Cases

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True priapism is a pathologic erection of the penis characterized by persistence, pain, and absence of libido. It has been recognized as an occasional symptom and complication of leukemia since Jadioux[1] reported the first case in 1845. Additional reports appeared sporadically, and by carefully reviewing the literature up to 1914, Hinman[2] collected a total of 45 cases with a definite relation to leukemia.

INCIDENCE

Approximately 25 per cent of the total cases of priapism are associated with leukemia. This association occurs in both the acute and the chronic form of myelogenous and lymphogenous leukemia, but appears much more frequently in the myelogenous.[3] The reported incidence of priapism in leukemia varies widely. Whereas Warthin[4] stated that he obtained a history of priapism in about one-fourth of his cases, Cabot[5] did not find a single instance of priapism in his series of 89 cases of leukemia. Craver[6] reported 1 case in 100 men with leukemia.

ETIOLOGY AND PATHOLOGY

The etiology of priapism in leukemia is nervous and mechanical. Kunst,[7] in support of nervous etiology, described a patient with hyperesthesia of the anal region, scrotum, and penis in whom priapism was relieved by supporting the spleen with an abdominal binder. He attributed priapism to compression of the sympathetics by the enlarged spleen. Ruh[8] suggested that a thrombus forming in the cord and disturbing the third, the fourth, and the fifth sacral segment might cause priapism. Barney[9] reported a case complicating leukemia in which priapism occurred after normal coitus. Postmortem studies by Warthin[4] and Ruh,[8] however, demonstrated that whatever the exciting cause, the persistence of priapism was due to a mechanical factor, which proved to be a leukemic thrombosis in the corpora cavernosa and dorsal veins of the penis. The glans was seldom involved in the process.

TREATMENT

For many years surgical treatment was advised. Either the congested blood was aspirated through a large needle, or the corpora were incised and the thrombi evacuated. Now, priapism persisting for forty-eight hours or longer and associated with leukemia is treated by deep x-ray therapy, which has been recommended by Kaplan,[10] Barney,[8] Archard,[11] Craver,[6] and others. When irradiation therapy is used, the leukemia is treated systemically, and additional radiation is directed to the penis.

CASE REPORTS

Case 1—A white man, aged 20, came to the clinic on June 10, 1942, complaining of abdominal pain and erection of the penis of ten days' duration. In October 1941 he had an attack of painful swelling of the ankles lasting one week. This condition, treated at home by bedrest, subsided spontaneously. After this he had frequent head colds throughout the winter. In May 1942 he had an attack of priapism, which disappeared twenty-four hours after administration of nembutal, gr. 1½. Ten days before admission to the clinic he had a severe, sharp pain in the left lower abdominal quadrant, which

radiated into the penis, the left side of the scrotum, and upper left thigh. This pain subsided in about three hours, but the next day the priapism recurred and was accompanied by painful swelling of the ankles. He entered the local hospital, and when the priapism failed to subside by the following day, the penis was incised without affording relief. Routine blood studies revealed an abnormal white blood cell count, and he was referred to this clinic for further treatment. The systemic history revealed anorexia and lassitude for three to four months, a weight loss of 8 pounds in one month, and diminished hearing in the left ear of seven days' duration.

The patient was a pale white man, well developed and well nourished, with normal temperature, pulse, and blood pressure. He had diminished hearing of the conduction type in the left ear. The teeth were carious. Firm, enlarged, but nontender lymph nodes were palpable in the cervical, inguinal, and left axillary regions. A large mass was palpable in the left upper abdominal quadrant and extended downward to the level of the umbilicus and medially to the midline. This mass was smooth with a sharp edge and indefinite tenderness. The penis was erect and very edematous and had a wound over each of the two lateral corpora cavernosa.

LABORATORY DATA

Urinalysis

Specific gravity—1.027
pH—7.5
No sugar, albumin, casts, red blood cells, or white blood cells

Blood analysis

Blood urea—51 mg. per 100 ml.
Fasting blood sugar—143 mg. per 100 ml.
Wassermann and Kahn—negative
Hemoglobin—9 Gm. per 100 ml.
Erythrocytes—3,200,000 per cu. mm.
Leukocytes—450,000 per cu. mm.
Color index—0.91

Differential

Neutrophils—53 per cent
Eosinophils—5 per cent
Basophils—2 per cent
Myelocytes—39 per cent
Myeloblasts—1 per cent

A diagnosis of myelogenous leukemia was made. The patient was admitted to the hospital immediately for deep x-ray therapy. In ten days he received a total of 400 r over the splenic area, 250 r over the penis and inguinal regions, and 175 r diffusely over the entire body. He was discharged on the eleventh hospital day. When seen one month later he was much improved, the penile erection had subsided, the spleen was no longer palpable, his appetite and strength had returned, and he was gaining in weight. The hemoglobin at this time was 10.5 Gm. per 100 ml., and leukocyte count was 11,950 with a differential of 77 per cent neutrophils, 1 per cent eosinophils, 4 per cent basophils, 11 per cent lymphocytes, 5 per cent monocytes, and 2 per cent myelocytes. He died December 1, 1943.

In addition to priapism this patient exhibited two other comparatively rare pathologic complications of leukemia, i.e., leukemic deafness and leukemic arthritis.

Case 2—A white man, aged 29, was first seen in the clinic on February 1, 1945, complaining of persistent, painful erection for three days. He was a toolmaker, worked at night, and for the past nine months was frequently awakened during the day by a sharp pain in his rectum. This pain was always followed by an erection of the penis, which was unaccompanied by any erotic sensation, persisted from three to ten hours, and then gradually subsided. Accompanying the erection he had a "bunched up" feeling in his rectum, and until he lost this sensation, he was unable to reduce the erection.

He attributed the erections to a hemorrhoidectomy performed in July 1943. The last attack of priapism persisted for three days, and when he came to the clinic, he carefully protected the erect organ from contact with his clothing. Systemic history was entirely negative except for moderate malaise and anorexia for two months. He had worked daily on a twelve hour shift until three days before admission.

Physical examination revealed a poorly nourished white man with a temperature of 100.4 F., pulse rate 116 per minute, and blood pressure measured in millimeters of mercury 144 systolic and 98 diastolic. The skin was hot, moist, and rather gray in color. Pupils reacted to light and in accommodation, but the retinal veins were somewhat engorged, and there was a small hemorrhage in each retina. No lymphadenopathy was noted. A large mass was palpable in the left upper quadrant of the abdomen, which extended downward to the umbilicus and medially to the midline and descended downward on inspiration. The edge was rounded, and the surface was smooth. The edge of the liver descended 2 cm. below the costal margin on deep inspiration. The penis was in a state of erection. The corpora cavernosa were very firm and quite tender. The prepuce was partially retracted exposing most of the glans, which was quite soft.

LABORATORY DATA

Urinalysis

Specific gravity—1.020
pH—5.3
Heavy trace of albumin
No sugar, casts, red blood cells, or white blood cells

Blood analysis

Blood urea—33 mg. per 100 ml.
Fasting blood sugar—88 mg. per 100 ml.
Wassermann and Kahn reactions—negative
Hemoglobin—10.5 Gm. per 100 ml.
Erythrocytes—4,670,000 per cu. mm. with a few nucleated red cells
Leukocytes—317,500 per cu. mm.
Color index—0.74

Differential

Neutrophils—64 per cent
Eosinophils—3 per cent
Basophils—4 per cent
Lymphocytes—1 per cent
Monocytes—1 per cent
Myelocytes—26 per cent
Myeloblasts—1 per cent

A diagnosis of chronic myelogenous leukemia was made. The patient was admitted to the hospital immediately for deep x-ray therapy. In a seven day period he received 100 r over the splenic area, 200 r over the penis and inguinal regions, and 200 r as an anterior body spray. He was discharged on his tenth hospital day with the penis somewhat reduced in size. When seen one month later he was greatly improved. The penis was flaccid, though somewhat tender, and perhaps slightly larger and somewhat firmer in consistency than normal. His appetite and strength had improved, and he was anxious to return to work. The spleen was just palpable. Hemoglobin was 12.5 Gm. per 100 ml., erythrocytes 5,040,000, and leukocytes 11,550 with a differential of 75 per cent neutrophils, 1 per cent eosinophils, 21 per cent lymphocytes, and 3 per cent monocytes.

COMMENT

Of the 309 men with leukemia seen in the clinic since 1930, only the two reported in this article had priapism as a complicating factor. This is an incidence of only 0.65 per cent. Both cases occurred in chronic myelogenous leukemia and represented an incidence of 3.2 per cent in the 62 cases of chronic myelogenous leukemia in men seen in this clinic.

The cause of the erection in both cases appeared to be nervous in origin. This view is supported by the presence of sharp pain radiating into the penis and scrotum and preceding the erection in case 1, and by the pain in the rectum preceding the erection in case 2. In both cases, however, there was thrombus formation in the corpora cavernosa, which resulted in persistence of the erection and pain.

In case 1 incision was attempted without success, whereas irradiation therapy resulted in relief of symptoms. In case 2 a satisfactory result was obtained by treating the leukemia systemically and the penis locally with deep x-ray therapy.

SUMMARY

1. In persistent priapism the presence of leukemia must be considered.

2. Priapism occurred as a complication of leukemia in only 0.65 per cent of the 309 cases in men seen in this clinic. However, it occurred in 3.2 per cent of men with chronic myelogenous leukemia.

3. The cause of priapism may be nervous in origin, but the persistence is undoubtedly due to thrombosis in the venous spaces of the corpora cavernosa.

4. Deep x-ray therapy given systemically for treatment of the leukemia and locally for the treatment of the priapism is the therapy of choice.

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